# Spiradenocarcinoma: a comprehensive data review

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Abstract: INTRODUCTION: Spiradenocarcinomas (SCs) are rare and potentially aggressive skin adnexal tumors. Optimal treatment has not yet been established. Experiences with this carcinoma are mostly presented in case reports and few case series. OBJECTIVE: To generate to a synopsis of published data on SC with regard to diagnostic procedures, treatment, and outcome. RESULTS: Median patient age was 60 years and sex distribution was balanced. Tumor manifestations were evenly distributed within the sweat gland carrying skin. The most commonly reported symptom was accelerated growth of a longstanding indolent lesion, typically present for more than 2 years. Metastatic spread to the lung, bone, lymph nodes, liver, kidney, and breast has been documented. For staging computed tomography (CT) and positron emission tomography-CT are recommended, especially for detection of hematogenic metastases and lymph node involvement. Clear resection margins and tumor free regional lymph nodes reduce recurrence and carcinoma related death. Although low-grade SCs were reported over 3 times more often, high-grade carcinomas show a greater likelihood for recurrence and lethal outcome. CONCLUSION: Suspicion of an SC should lead to performance of a magnetic resonance imaging for defining tumor extent, and a fludeoxyglucose positron emission tomography-CT for detection of metastases. Radical tumor excision and resection of tumor involved regional lymph nodes are essential for a curative approach. Histopathological evaluation should involve determination of tumor differentiation grade, because high-grade carcinomas seem to have a much more aggressive behavior. Excision of distant metastases has no therapeutic value. Follow-up needs to be carried out in short intervals with frequent imaging.

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# Spiradenocarcinoma: A Comprehensive Data Review

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**Objective:** To generate to a synopsis of published data on SC with regard to diagnostic procedures, treatment, and outcome.

**Results:** Median patient age was 60 years and sex distribution was balanced. Tumor manifestations were evenly distributed within the sweat gland carrying skin. The most commonly reported symptom was accelerated growth of a longstanding indolent lesion, typically present for more than 2 years. Metastatic spread to the lung, bone, lymph nodes, liver, kidney, and breast has been documented. For staging computed tomography (CT) and positron emission tomography-CT are recommended, especially for detection of hematogenic metastases and lymph node involvement. Clear resection margins and tumor free regional lymph nodes reduce recurrence and carcinoma related death. Although low-grade SCs were reported over 3 times more often, high-grade carcinomas show a greater likelihood for recurrence and lethal outcome.

**Conclusion:** Suspicion of an SC should lead to performance of a magnetic resonance imaging for defining tumor extent, and a fludeoxyglucose positron emission tomography-CT for detection of metastases. Radical tumor excision and resection of tumor involved regional lymph nodes are essential for a curative approach. Histopathological evaluation should involve determination of tumor differentiation grade, because high-grade carcinomas seem to have a much more aggressive behavior. Excision of distant metastases has no therapeutic value. Follow-up needs to be carried out in short intervals with frequent imaging.

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## LEARNING OBJECTIVES

Spiradenocarcinomas are rare and potentially aggressive adnexal neoplasms evolving from benign spiradenomas. Due to their scarcity guidelines for the optimal treatment of these cancers have not been determined so far. This CME article is intended to call attention to the clinical presentation and pathological and immunehistological features of spiradenocarcinomas; it also provides recommendations for their diagnostics, treatment, and follow-up.

After participating in this CME activity participants should be able to:

1. Explain the role and application of medical imaging, surgical resection, adjuvant treatments, and follow-up for treatment of spiradenocarcinomas.
2. Describe the main histopathological and immunehistochemical features of spiradenocarcinoma for diagnostics and prognostics.
3. Name possible preventive measures.

## INTRODUCTION

Spiradenocarcinomas (SCs), also referred to as malignant eccrine spiradenomas,[1–3] are rare malignant adnexal neoplasms arising from a benign spiradenoma of the eccrine sweat gland.[1] They are presumed to be highly aggressive. However, in the recent literature a more favorable clinical course in cases with low-grade histomorphological features has been reported.[4–6] The eccrine spiradenoma is considered the primary skin lesion from which an SC evolves, but de novo appearances have been reported as well.[7–9] Accelerated growth of a long-standing lesion, pain, and ulceration are the most common symptoms that lead to referral. Bluish discoloration and impairment resulting from tumor growth have also been described.[3,10–12] A connection to the Brooke–Spiegler Syndrome, an autosomal dominant genetic disorder, phenotypically characterized by multiple skin tumors, such as spiradenomas, cylindromas, trichoepitheliomas, and tumors of the parotid gland, is suspected.[13–15] The tumor suppressor gene CYLD, located on chromosome 16q12-q13 has been identified by genetic studies to encode for hereditary transmission of multiple familiar cylindromas as well as its associated tumors arising from skin appendices and the parotid gland.[16–18]

One hundred twenty cases of SC have been published up to December 2015, most of them as case reports. Because

of its rarity the optimal treatment for SC is unclear. Our own difficulties with a patient with SC and the absence of guidelines for treatment have led to the objective to summarize the published data to find some guidance for diagnosis, treatment, and follow-up of SCs.

## LITERATURE REVIEW

### Materials and Methods

PubMed was searched for the key words "spiradenocarcinoma" (All Fields) and "malignant spiradenoma" (All Fields) up to December 31, 2015. This led to 151 matching results: 34 cases with the key word "spiradenocarcinoma" and 117 with "malignant spiradenoma." Included in this review were reports with a histopathological diagnosis of SC, malignant spiradenoma, or with malignant differentiation of a spiradenoma. Reports of tumors consisting of a combination of different skin adnexal carcinomas (21), duplicate reports (11), and studies in which data concerning SCs could not be distinguished from other skin adnexal tumors (7) were excluded. One hundred twenty patients were presented in 71 case reports[3,6–12,15–50,51–80] and 3 case series.[5,14,81] Each case report was analyzed for patient's age, sex, and ethnicity. Tumor characteristics were collected regarding size, location and duration of presence, symptoms as well as their existence until presentation. We extracted clinical data concerning treatment, staging, and histopathological features including immunehistochemical profile if available. Further, information on the clinical course, such as tumor recurrence, location of recurrence, time span between primary tumor and recurrence as well as its therapeutic approach was gathered. We added our own case to the analysis (Table 1).

**TABLE 1.** Case Report SC, Limmattal Hospital, Zurich-Schlieren, Switzerland

| Case Report |
|---|
| Patient |
| 44 year old female, white |
| Tumor |
| Upper back |
| Small lesion present since 15 yrs |
| 50 × 80 × 40 mm |
| Clinical findings |
| Duration of symptoms: 1 mo |
| Fast growing |
| Ulceration |
| Bluish discoloration |
| Preoperative examinations |
| Biopsy |
| MRI |
| Sonography breasts/axillary region |
| Mammography |
| PET/CT 320 MBq$^{18}$ F-FDG |
| Therapy |
| Radical tumor excision (10 mm margin) |
| Bilateral axillary lymphnodectomy level I and II |
| Pathological features |
| Poorly differentiated spiradenocarcinoma, vascular invasion |
| Surgical margins tumor free |
| TNM classification pT2, V1, G3, R1. |
| Small basophil cells with an isomorph nucleus, few mitotic figures |
| Tubulo-glandular and hyalinized eosinophil stroma |
| Immunehistochemical features |
| CK 5/6, 7: positive (weak) |
| EMA: positive |
| p63 and p40 antibodies: positive (few) |
| Expression of estrogen receptor: 10% of tumor cells (weak) |
| C-KIT: positive; KIT mutation analysis: negative. |
| TP53: pR273C mutation: 34% |
| Follow-Up |
| 15 Mt. (death) |
| Recurrence and therapy |
| 5 Mt. post initial surgery: 5 mm nodule upper lobe right lung |
| → Wedge resection |
| 12 Mt. pleural tumor mass growth through anterior right thorax wall into right mammary with rib arrosion |
| → Palliative chemotherapy: Imatinib |
| → Palliative radiotherapy of the bone metastases |

CK, cytokeratin; C-KIT, tyrosine-protein kinase; EMA, epithelial membrane antigen; F-FDG, fludeoxyglucose; MBq, megabecquerel; TP53, tumor protein p53.

## RESULTS

### Epidemiology and Clinical Findings

The epidemiology and clinical details of the published data is presented in Table 2. The median patient age was 60 years (range 8–92 years). SC occurred in 58 women (47.9%) to 44 men (36.3%). The ethnicity of the patient was rarely documented (17.3%). Tumor localization was equally distributed throughout the sweat gland carrying skin. The median tumor size at presentation was 3 cm (range 0.8–25 cm). Duration of presence of a previous lesion ranged from 2 months to 80 years (median 6.5 years). The most common tumor symptoms were growth acceleration, pain, and ulceration. Bluish discolorations and bleeding ulcers were also mentioned. In 5 cases the tumor mass caused impairment (ataxia, palsy, hearing loss, ptosis, or lymph edema) because of its size.[8,11,12,19,55] Duration of symptoms ranged from 1 week to 4 years (median 4 months).

### Diagnostics and Staging

Overall, diagnostic procedures and staging were poorly documented. The final diagnosis was based on the histopathological examination of an excisional biopsy or surgical resection specimen. Imaging procedures, including computed tomography (CT) scan (15/121), magnetic resonance imaging (MRI) (9/121), positron emission tomography-CT(PET-CT) (6/121), chest x-ray (4/121) and ultrasound (4/121), and scintigraphy of the lymphatic drainage (2/121) area were used for staging. Furthermore, one patient received a mammography, because of the tumor biopsy's histological pattern's similarity to mammary gland tissue.

**TABLE 2.** Summary of Epidemiological and Clinical Information

| Epidemiological and Clinical Information | Total Cases Available Data (% of Total Cases) | Recurrence-Free Survival (% of Total Cases) | Recurrence (% of Total Cases) | Death (% of Total Cases) |
|---|---|---|---|---|
| Total cases | 121 (100) | 45 (37.2) | 21 (17.4) | 13 (10.2) |
| Age (Median), yrs | 60 (8–92) | 63 (21–92) | 59.5 (30–72) | 70 (44–89) |
| Sex | 102/121 (84.3) | 43 (42.2) | 18 (17.6) | 12 (11.8) |
| Female | 58/102 (56.9) | 20 (35.5) | 12 (20.7) | 5 (8.6) |
| Male | 44/102 (43.1) | 23 (52.3) | 6 (13.6) | 7 (15.9) |
| Ethnicity, n (%) | 21/121 (17.4) | 8 (38.1) | 5 (23.8) | 3 (14.3) |
| White | 12/21 (57.1) | 6 (50.0) | 2 (16.7) | 2 (16.7) |
| African/African American | 4/21 (19.0) | 0 (0) | 2 (50.0) | 1 (25.0) |
| Asian | 3/21 (14.3) | 2 (66.7) | 1 (33.3) | 0 (0.0) |
| Indian | 2/21 (9.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Tumor location | 106/121 (87.6) | 43 (60.6) | 19 (17.9) | 12 (11.3) |
| Head (face, scalp, neck) | 39/106 (36.8) | 13 (33.3) | 8 (20.5) | 8 (20.5) |
| Trunk (chest, back, abdomen, pelvis) | 29/106 (27.4) | 12 (41.4) | 4 (13.8) | 1 (3.4) |
| Extremities (incl. hand, foot) | 38/106 (35.9) | 18 (47.4) | 5 (13.2) | 1 (2.6) |
| Side of the body | 41/121 (33.9) | 22 (53.7) | 6 (14.6) | 1 (2.4) |
| Left | 19/41 (46.3) | 10 (52.6) | 2 (10.5) | 0 (0.0) |
| Right | 22/41 (53.7) | 12 (54.5) | 4 (18.2) | 1 (4.5) |
| Tumor size (Median), cm | 3 (0.8–25) | 3 (0.8–25) | 4 (0.8–12) | 5.5 (1–10) |
| Time lesion present before symptoms, yrs | 0.17–80 | 8 (0.17–80) | 9 (2–50) | 4 (0.17–15) |
| ≤2 | 20/66 (30.3) | 9 (45.0) | 1 (5.0) | 2 (10.0) |
| >2 | 46/66 (69.7) | 18 (39.1) | 9 (19.6) | 3 (6.5) |
| Symptoms | 64/121 (52.9) | 28 (43.8) | 23 (35.9) | 10 (15.6) |
| Growth | 60/64 (93.8) | 24 (40.0) | 13 (21.7) | 6 (10.0) |
| Pain | 15/64 (23.4) | 7 (46.7) | 5 (33.3) | 0 (0.0) |
| Ulceration | 13/64 (20.3) | 6 (46.2) | 2 (15.4) | 2 (15.4) |
| Bluish discoloration | 4/64 (6.3) | 1 (25.0) | 1 (25.0) | 0 (0.0) |
| Bleeding | 4/64 (6.3) | 2 (50.0) | 1 (25.0) | 1 (25.0) |
| Disabilities | 5/64 (7.8) | 1 (20.0) | 1 (20.0) | 1 (20.0) |
| Duration of symptoms | 0.25 mo–4 yrs | 8 mo (0.25 mo–4 yrs) | 1 mo (1–23 mo) | 2 mo (1–4 mo) |

## Pathologic and Immunohistochemical Findings

Table 3 presents the pathological data. Tumor grading was reported in 30% (36/121) of all cases. As histopathologic criteria for such classification antigen KI-67 staining was reported in 58.3% (21 cases), mitotic rate in 36.1% (13 cases), and no statement was made in 5.5% (2 cases). Tumor grade was high in 19% (4/21) of cases with tumor recurrence and in 23% (3/13) of the patients who died during follow-up. Furthermore, a wide range of different immunehistochemical markers was tested. SCs are positive for most cytokeratins with CK 5–7 most frequently being reported. Also tumor protein p53 was found positive in 90% (28/31); estrogen receptors were rarely screened for with 63% being negative (5/8).

## Treatment

Tumor resection was the primary treatment for all patients; too advanced tumor progression for complete surgical resection was the only exception. Surgical excision of the afflicted lymphatic nodes was performed in 83% (10/12), in patients with extensive tumor spread a lymphnodectomy was refrained from. In addition to tumor resection, further treatment was described in 6 case reports. Three patients received adjuvant radiotherapy,[10,20,66] one of them in combination with chemotherapy.[62] For the first patient no follow-up or outcome after radiotherapy was described.[10] For the second patient, a 6 months recurrent free survival after radiotherapy (dosage unknown) was reported.[20] In the third case a total dosage of 59.4 Gray (Gy) over 64 days onto the tumor bed was applied and 45 Gy over 35 days onto the inguinal and pelvic nodes. Tumor recurrence at the primary tumor location without distant metastases occurred 9 months later. Despite a wide tumor excision with lymphadenectomy and hyperthermic isolated limb perfusion chemotherapy lung metastases occurred 3 months later; the patient died 20 months after initial diagnosis.[66]

Four patients underwent adjuvant chemotherapy. The agents used were 5-FU,[66] Tamoxifen[3] Epirubicin,[7] and Ifosfamide.[7] The fourth patient was already under chemotherapy treatment because of an adenocarcinoma of the colon with liver metastases.[70] All patients were diagnosed with distant metastases or died within 4 months. The exception was, a patient treated with a continuous Tamoxifen therapy after tumor resection and lymphnodectomy of an estrogen receptor positive SC of the upper arm. No tumor recurrence was found after 41 months of follow-up.[3]

**TABLE 3.** Summary of Reported Pathologic and Immunehistochemical Findings

| Pathologic and Immunehistochemical Findings | Total Cases Available Data (% of Total Cases) | Recurrence-Free Survival (% of Total Cases) | Recurrence (% of Total Cases) | Death (% of Total Cases) |
|---|---|---|---|---|
| Total cases | 121 (100) | 45 (37.2) | 21 (17.4) | 13 (10.2) |
| SC grading | 36/121 (29.8) | | | |
| High | 8/36 (22.2) | 2 (25.0) | 4 (50.0) | 3 (37.5) |
| Low | 28/36 (77.8) | 21 (75.0) | 4 (14.3) | 4 (14.3) |
| Cytokeratins | | | | |
| Positive | 13/121 (10.7) | 7 (53.8) | 5 (38.5) | 3 (23.1) |
| CK 5 | 3/121 (2.5) | 2 (66.75) | 1 (33.3) | 1 (33.3) |
| CK 6 | 2/121 (1.7) | 1 (50.0) | 1 (50.0) | 1 (50.0) |
| CK 7 | 7/121 (5.8) | 3 (42.9) | 4 (57.1) | 3 (42.9) |
| Cytokeratin antibodies | | | | |
| AE1 | 5/121 (4.1) | 4 (80.0) | 1 (20.0) | 0 (0.0) |
| AE3 | 5/121 (4.1) | 4 (80.0) | 1 (20.0) | 0 (0.0) |
| CAM 5.2 | 3/121 (2.5) | 2 (66.75) | 1 (33.3) | 0 (0.0) |
| Proteins | | | | |
| p53 | 28/121 (23.1) | 23 (82.1) | 2 (7.1) | 4 (14.3) |
| Receptors | | | | |
| Estrogen receptors | 3/121 (2.5) | 2 (66.75) | 1 (33.3) | 1 (33.3) |
| Progesterone receptor | 1/121 (0.8) | 1 (100) | 0 (0.0) | 0 (0.0) |
| Others | | | | |
| MYB | 2/121 (1.7) | 1 (50) | 0 (0.0) | 1 (50.0) |
| c-KIT | 1/121 (0.8) | 0 (0) | 1 (100) | 1 (100) |
| EMA | 13/121 (10.7) | 10 (76.9) | 2 (15.4) | 2 (15.4) |

c-KIT, tyrosine-protein kinase kit; EMA, epithelial membrane antigen.

## Outcome

Oncological outcome is shown in Table 4. With a median follow-up time of 24 months, the total recurrent free survival was 37% (45/121), cases with tumor recurrence were reported in 17% (21/121), and the documented occurrence of death in 10% (13/121). The nodal status and local recurrence was rarely described. From the reported data, the median of 12 months follow-up time until tumor recurrence (range 1 month–7 years) was calculated. Those patients had tumor free resection margins in 67% (6/9); of the ones who died during follow-up R0 resection was described in 40% (2/5). Lung, bone, and lymph nodes were the most frequently reported locations of metastatic spread. Few cases of liver-, kidney-, and breast metastases have also been documented. Of the 13 deaths during follow-up, 3 patients died shortly after the surgery (1–8 weeks) and 5 showed tumor recurrence before death (recurrence 5–84 months).

## DISCUSSION

The first case of an SC was reported in 1971 by Dabska.[30] Because of the low incidence of SC only few case series are available, each with less than 20 patients.[5,14,81] This results in a great variability of published data and makes a meaningful statistical analysis of the gathered information impossible.

The epidemiological features of SC are unspecific. SC occur predominately in the elderly patient (median age 60 years), however a wide range in patient age has been reported throughout the literature (8–92 years).[53,72] There is no specific sex distribution of SC.[8,15,81] Our data summary do not support the suspicion of a predominance of the tumor localization in the head, neck, and trunk region that was suggested in previous reports.[14,66,81] The large sized carcinomas' (>10 cm) main symptom was painless growth; therefore, medical consultation may have been delayed, allowing the tumor to reach such an extent. A lesion was often present for many years, before rapid growth, sometimes in combination with pain, ulceration, or less common, bleeding or discoloration occurred.[14,15,44] Therefore, we recommend the preventive excision of every diagnosed spiradenoma.

Preoperative investigations were rarely documented and consisted mostly of CT scans or MRI for determination of the extent of tumor infiltration. The few authors who added a PET/CT scan to their staging procedure[3,10,28,53,60] describe a notable gain of valuable information regarding the presence and location of metastases, especially if clinical findings were unremarkable. Fludeoxyglucose (FDG) PET/CT imaging is known to have high sensitivity for detection of metastases of skin tumors,[82,83] particularly for primary apocrine sweat gland carcinomas and eccrine porocarcinomas.[84,85] The proportion of FDG sensitive SC is unknown.

Not only was the follow-up period mostly brief, also further treatments and course of illness were barely reported once a recurrence occurred. Specific tumor markers have not been identified yet. The impact of tumor free resection margins regarding tumor recurrence or survival is unclear.[2,66,81] Our data, however, show fewer recurrences and deaths after tumor

**TABLE 4.** Outcome Summary

| Outcome | Total Cases Available Data (% of Total Cases) | Recurrence-Free Survival (% of Total Cases) | Recurrence (% of Total Cases) | Death (% of Total Cases) |
|---|---|---|---|---|
| Total cases | 121 (100) | 45 (37.2) | 21 (17.4) | 13 (10.2) |
| Follow-up time (Median), mo | 24 | 24 | 10 | 15 |
| Resection margins | 33/121 (27.3) | | | |
| R0 resection | 26/33 (78.8) | 18 (69.2) | 6 (23.1) | 2 (7.7) |
| R1 resection | 7/33 (21.2) | 1 (14.3) | 3 (42.9) | 3 (42.9) |
| Lymph node status | 26/121 (21.5) | | | |
| Positive lymph nodes | 13/26 (50) | 7 (53.8) | 4 (30.8) | 2 (15.4) |
| Negative lymph nodes | 13/26 (50) | 11 (84.6) | 2 (15.4) | 0 (0.0) |
| Metastatic spread | 23/121 (19.0) | | | |
| Lung | 8/23 (34.8) | | | |
| Bone | 6/23 (26.1) | | | |
| Lymphatic drainage | 5/23 (21.7) | | | |
| Liver | 2/23 (8.7) | | | |
| Kidney | 1/23 (4.3) | | | |
| Breast | 1/23 (4.3) | | | |
| Recurrence location | 21/121 (17.3) | | | |
| Tumor bed | 5/21 (23.8) | | | |
| Other location | 11/21 (52.4) | | | |
| Death | 13/121 (10.7) | | | |
| w/recurrence | 5/13 (38.5) | | | |
| w/o recurrence | 8/13 (61.5) | | | |

R0 resection, tumor free resection margins; R1 resection, tumor reaches resection margins; w/, with; w/o, without.

resection with tumor free margins compared with R1 resections (recurrence 23% vs. 43%), (death 8% vs. 43%). Regional lymph node excision has been recommended for tumor positive regional lymph nodes[2,3] and sentinel node biopsy is considered useful in clinically unsuspicious ones.[2] However, the benefit of routine locoregional lymph node dissection is unknown and therefore not advised.[66,81] Our recommendation for radiological SC diagnostics and staging include MRI for defining the tumor extent and FDG PET/CT for the detection of metastases. For treatment, we strongly advice to obtain tumor free resection margins and recommend the resection of tumor positive lymph nodes. Follow-up should include recurrent imaging; frequency may be broadened over time.

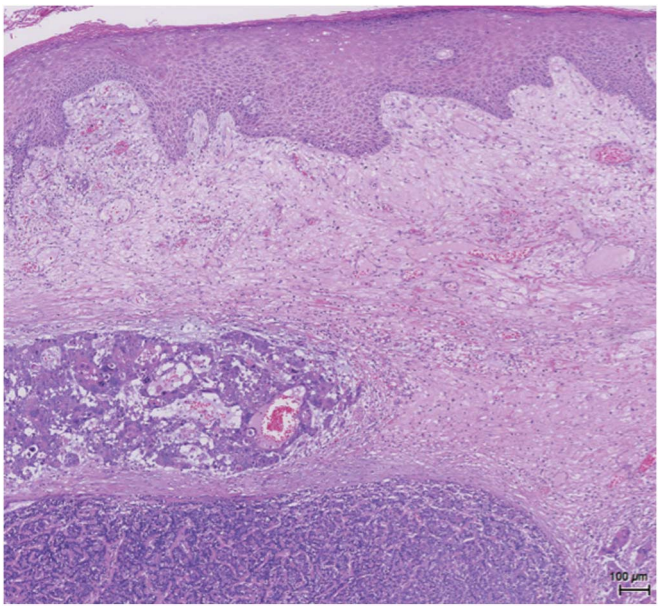


**FIGURE 1.** Overview: Squamous cell epithelial layer, subepithelial area with high-grade SC, underneath a defined zone with features of a spiradenoma. Case of an SC of a 44-year-old white woman, Limmattal Hospital, Zurich-Schlieren, Switzerland (Table 1).

Per definition, for the diagnosis of an SC areas of benign spiradenoma must be found adjacent to the malign transformation in the pathological examinations[1] (Fig. 1). The current WHO classification describes 2 major histologic patterns; one shows a continuous transformation from benign to malignant neoplasm, in the other the malignant transitions are adjacent to the spiradenoma without structural or cytological changes[1] (Fig. 2). De novo appearances of SC have been described[7–9]; they are an explicit rarity, because the malignant degeneration would need to be concurrent with the primary growth of the spiradenoma. Further, an interrelation between spiradenoma, cylindroma, and spiradenocylindroma has also been reported.[4,86] In the 2009, published case series on adnexal skin tumors,[4] 4 histomorphological patterns and their correlation with clinical behavior and prognosis were described: salivary gland type basal cell adenocarcinoma-like pattern low-grade (BCAC), salivary gland type BCAC high-grade, invasive adenocarcinoma not otherwise specified, and sarcomatoid (metaplastic) carcinoma. Considering the long-term-survival rates of 50% for skin adnexal tumors with

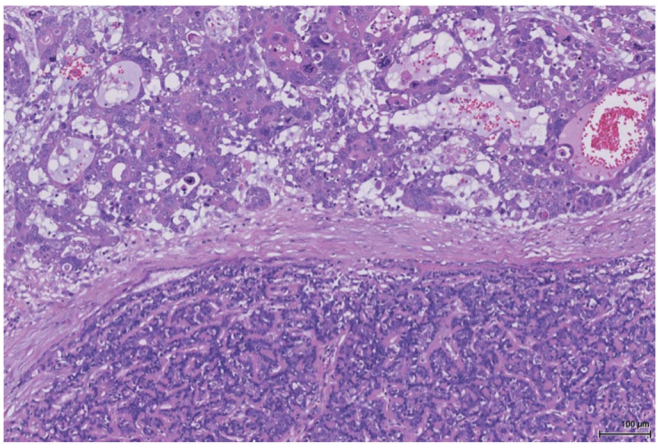

**FIGURE 2.** Magnification: Well-differentiated spiradenoma at the bottom featuring an abrupt transition to a high-grade SC with numerous atypical mitotic figures (WHO classification 2). Case of an SC of a 44-year-old white woman, Limmattal Hospital, Zurich-Schlieren, Switzerland (Table 1).

the histomorphological pattern of BCAC high-grade reported in this study, these neoplasms seem to be more aggressive compared with the BCAC low-grade type (100% long-term survival).[4,14] Also invasive adenocarcinoma not otherwise specified carcinomas are considered highly malignant neoplasms with rather poor outcomes, whereas sarcomatoid carcinomas show a relatively good survival.[4] However, this histopathologic classification for skin adnexal tumors is not commonly used yet.

Only in 30% of the published SC cases a tumor grade is declared; most of them being low-grade carcinomas (28 vs. 8 cases). Corresponding with previous findings, our data show a higher incidence regarding tumor recurrence and death in high-grade carcinomas (recurrence 50% vs. 14%, death 38% vs. 14%) compared with reported low-grade SC (Table 3).[4,5,14] Some SC feature spindle cells, giving a sarcomatid appearance to the neoplasm [4]; however, mostly these tumors lack distinctive morphological features and hold no specific immunological profile. SCs are positive for most cytokeratins; also estrogen and progesterone receptor expression are occasionally found, presumably because of the common embryologic origin of eccrine sweat glands and mammary gland tissue.[9] Mutations in the TP53 gene is a known indicator for malignant transformation,[87] however, there is no obvious correlation between the TP53 mutation status and the p53 tumor suppressor protein expression.[88] Although strong p53 expression has been reported for SC,[87] these tumors typically lack mutations in the TP53 gene.[5] Furthermore, immunohistochemical staining for p53 appears to be heterogeneous; therefore, it cannot be reliably applied for identification of malignant transformed areas.[5,88] One recent case series analyzed 19 SC cases for myeloblastosis protein (MYB),[5] a proto-oncogene protein that plays an important role in proliferation, apoptosis, and differentiation of cells.[89] Although detected in spiradenomas, MYB is absent in its malign transformation, regardless if high or low grade. Therefore it may serve as an additional immunehistochemical marker for the distinction between spiradenoma and its low-grade malignant transformation.[5,90] Our recommendations for pathologic evaluations of a suspected SC are first, the verification of SC according to the 2 major histologic patterns,[1] second, the determination of the tumor differentiation grade for a more accurate estimation of the patient's prognosis and third, MYB staining for determination of malignant differentiation of a spiradenoma by histomorphologic uncertainty.

No data on the optimal management strategy concerning distant metastases or on a satisfactory response of radiotherapy or chemotherapy has been published.[3,14,41,53] There are known cases of adenoid cystic carcinomas, a type of malign sweat gland tumor, responding to chemotherapy with Imatinib.[91,92] This protein kinase inhibitor targets c-KIT, which is expressed in a variety of malignant tumors, such as gastrointestinal stromal tumor, malignant melanoma or adenoid cystic carcinoma of the salivary gland.[86,93] A recent study further investigated benign and malignant sweat gland tumors according to their c-KIT expression.[86] Although immunehistochemical positivity to c-KIT was present in most analyzed sweat gland tumors, only the adenoid cystic carcinomas showed a population of c-KIT positive cells big enough for a useful Imatinib therapy.[86] Furthermore, Tamoxifen, a selective estrogen receptor modulator, has been tried as an adjuvant therapy in a case of estrogen receptor positive SC.[3] No tumor recurrence was stated for 41 months.[3] Because of the common embryologic tissue origin,[9] estrogen receptors may not only be found in mamma carcinomas, but also in rare cases of SC.

Radiotherapy of the tumor site has been recommended in the past[36,74,79] but was hardly performed in the literature. A literature review from 1986 has declared sweat gland tumors to be radioresistant, consequently little significance was granted to radiotherapy as treatment of such carcinomas.[94] Therefore, Tamoxifen therapy for those rare cases of estrogen receptor positive SC is the only useful recommendation regarding adjuvant therapy.

## CONCLUSION

Inferred from the available data, suspicion of a SC should lead to performance of an MRI for defining tumor extent and FDG PET/CT for detection of metastases. The main pilar of treatment is radical tumor excision and the resection of tumor involved regional lymph nodes. Histopathological evaluation should involve determination of tumor differentiation grade for prognosis estimation; high-grade carcinomas seem to have a much more aggressive behavior compared with low-grade SC, which carry the potential for cure. To evaluate the possibility of an adjuvant Tamoxifen therapy, staining for estrogen receptors is recommended. Excision of distant metastases has no therapeutic value, but may be done for symptom alleviation. Follow-up needs to be carried out in short intervals with frequent imaging. To assess the influence of each clinical, radiological, or histopathological parameter regarding patient's outcome, a prospective uniform international data collection would be required.

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## CME EXAMINATION
## October 2017

Please mark your answers on the ANSWER SHEET.

After participating in this CME activity participants should be able to explain the role and application of medical imaging, surgical resection, adjuvant treatments, and follow-up for treatment of spiradenocarcinomas, describe the main histopathological and immunehistochemical features of spiradenocarcinoma for diagnostics and prognostics, name possible preventive measures.

1. Which statement regarding surgical treatment of spiradenocarcinomas is true?

   a. Resection margin of 1 cm is imperative for prevention of local tumor recurrence
   b. R0 resection (tumor free resection margins) is associated with lower tumor recurrence
   c. Excision of tumor positive regional lymph nodes has no impact on the course of the disease
   d. Resection of distant metastases decelerates disease progress

2. Which statement for diagnostics or nonsurgical treatment of spiradenocarcinomas is true?

   a. Tumor staging should include PET/CT for diagnosis of metastases
   b. Yearly clinical check ups are the current recommendations for follow-up after surgical resection of spiradenocarcinomas
   c. The combination of chemotherapy and radiotherapy is a promising adjuvant therapy
   d. Neoadjuvant Tamoxifen therapy increases recurrent free survival rate

3. Which statement of the pathological features of spiradenocarcinomas is true?

   a. The histologic pattern of a spiradenocarcinoma always shows a continuous transformation from benign to malignant neoplasm
   b. Spiradenocarcinoma have distinctive morphological features
   c. The quantity of atypical mitotic figures has no influence on the prognosis
   d. Essential for the diagnosis of spiradenocarcinoma a part of benign spiradenoma must be found adjacent to the area of malign transformation

4. All of the following pathological or immunehistological findings can be detected in spiradenocarcinomas. Which of them has the greatest significance for prognostics?

   a. p53 tumor suppressor protein expression
   b. Mitotic figure count
   c. Presence of estrogen/progesterone receptors
   d. MYB staining

5. Which of the following approaches is the most promising preventive measure for spiradenocarcinomas?

   a. Frequent clinical follow-up of diagnosed spiradenomas
   b. Preventive Tamoxifen therapy
   c. Preventive excision of ascertained spiradenomas
   d. No preventive measure can be taken

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| 1. Explain the role and application of medical imaging, surgical resection, adjuvant treatments, and follow-up fortreatment of spiradenocarcinomas | O O O O O | O O O O O |
| 2. Describe the main histopathological and immunehistochemical features of spiradenocarcinoma for diagnostics and prognostics | O O O O O | O O O O O |
| 3. Name possible preventive measures | O O O O O | O O O O O |

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o For maintenance of licensure

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